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A CONTRIBUTION TO THE THEORY OF ANAPHYLACTIC SHOCK*

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PLATE 4.

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Doerr and Russ,[1] and Doerr and Moldovan[2] demonstrated that there exists a parallelism between the amount of precipitins in immune serum and its power to provoke the state of passive anaphylaxy in normal animals. Friedemann[3] observed the same dependence between this power and the content of hemolysins in the serum. Scott[4] proved that the intensity of the anaphylactic shock is proportionate (in a sensitized animal) to the content of precipitins in its serum, these precipitins being consumed during the shock. Though one cannot affirm with certitude the identity of the precipitins and hemolysins on the one hand, and the antibodies provoking the anaphylactic shock on the other, yet these data, confirmed by other workers, show that the parallelism of their existence is an undisputable fact.

In several articles[5] I have presented the results of my observations and experiments concerning the proprieties of the juice of a plant, Cotyledon scheideckeri, which is able to precipitate animal serum and bacterial extracts, to agglutinate bacteria and blood corpuscles, and to lake the latter. Now, with a view to the facts stated by Friedemann, Doerr and Russ, Doerr and Moldovan, and Scott, I undertook to solve the problem, whether the cotyledon juice, possessing such an influence over serum and animal cells, has the power to provoke the clinical and anatomic changes characteristic of anaphylactic shock, when introduced into the living animal. This is the object of the present investigation. The experiments gave a positive answer. The guinea-pigs and rabbits which received the fluid intravenously died; the clinical picture and the anatomic changes were those of anaphylaxis.

The clinical phenomena are generally as follows: The guinea-pig after being taken from the table (this requires 15-25 seconds) remains

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[1] Ztschr. f. Immunitätsforsch., 1909, 3, p. 706.

[2] Ibid., 1910, 2, p. 161.

[3] Ibid., 1909, 2, p. 591.

[4] Jour. Path. and Bacteriol., 1910, 14, p. 147.

[5] Ztschr. f. Immunitätsforsch., 1914, 22, p. 381; 1915, 23, p. 321.

very quiet for some time, generally 15-45 seconds; only now and then it has a brief chill; then begin tonic and clonic convulsions of the muscles of the extremities, the trunk and the neck, during which the animal falls on its side. The period of convulsions is followed by dyspnea, lasting a longer time than the preceding phase and ending with death in a comatose state. The intervals between the respiratory movements grow each time longer; finally, the act of breathing becomes a catching and swallowing of the air. The reflexes of the cornea gradually disappear. In this period urine is often voided. Sometimes convulsive wormlike movements of the paws are observed. In some cases a foaming liquid tinged with blood comes from the mouth and nostrils the moment before death.

Rabbits offer a similar picture. An intense opisthotonus is frequently observed; sometimes the head is turned up almost at a right angle to the body, and in this position the animal dies. Often the rabbit gives a scream during the dyspnea. Now and then the dyspnea does not appear at all; but exophthalmus is always observed.

EXPERIMENT 1

Only the facts which vary from one experiment to another are mentioned in the protocols.

GUINEA-PIGS

1. Weight, 340 gm.; 10 c.c. Cotyledon Fluid 5 into jugular vein; died in 2 minutes; lungs greatly inflated, emphysematous; no thrombi.
2. Weight, 340 gm.; 8.5 c.c. Fluid 5 into jugular vein; death in 3 minutes; lungs greatly distended, punctate hemorrhages; thrombus in right heart.
3. Weight, 340 gm.; 5 c.c. Fuid 5 into jugular vein; no effect.
4. Weight, 310 gm.; 6 c.c. Fluid 8 into jugular vein; death in 4½ minutes; lungs greatly inflated; thrombus in right heart.
5. Weight, 305 gm.; 4 c.c. Fluid 8 into jugular vein; died in 3 minutes; strongest lung inflation; thrombus in right and left heart.
6. Weight, 310 gm.; 2 c.c. Fluid 8 into jugular vein; no effect.
7. Weight, 370 gm.; 10 c.c. Fluid 10 into jugular vein; death in 3 minutes; moderate lung inflation; no thrombosis in heart cavities; thrombus in inferior vena cava.
8. Weight, 375 gm.; 6 c.c. Fluid 10 into jugular vein; death in 2½ minutes; strong lung inflation; thrombus in right heart.
9. Weight, 375 gm.; 4 c.c. Fluid 10 into jugular vein; fell on side and convulsions; after 1½ minutes it recovered and arose; 5½ minutes after injection it fell again; convulsions, dyspnea, and death in 2 minutes. No thrombus in heart cavities nor lungs; no lung inflation.
10. Weight, 380 gm.; 2 c.c. of Fluid 10 into jugular vein; no effect.
11. Weight, 405 gm.; 4 c.c. Fluid 9 into jugular vein; no effect during first 3 minutes; then convulsions; yet after 2 minutes the animal recovered.

12. Weight, 360 gm.; 6 c.c. Fluid 9 into jugular vein. Death in 2 minutes; strong lung inflation; thrombus in right heart.

13. Weight, 360 gm.; 4 c.c. Fluid 12 into jugular vein immediately after taking 4 c.c. of blood from the heart. Death followed in 3 minutes; no lung inflation; the thorax was full of blood and clots; no thrombus in the heart cavities.

14. Weight, 355 gm.; 6 c.c. of Fluid 12 into jugular vein immediately after 4 c.c. of blood were taken from the heart; death after 2½ minutes; slight lung inflation; no thrombus in the heart.

15. Weight, 355 gm.; 4 c.c. of Fluid 14 into jugular vein; death after 2 minutes; strong lung inflation; thrombus in right heart; before the experiment 4 c.c. of blood were taken from the heart.

16. Weight, 515 gm.; 6 c.c. Fluid 14 into jugular vein. No effect during 15 minutes; then began convulsions; the pig fell on its side; after the short convulsive period there followed dyspnea and a deep comatose state, which lasted 55 minutes; death after 71 minutes from the beginning of the experiment; no lung inflation; no thrombus in the heart.

17. Weight, 470 gm.; 4 c.c. Fluid 16 into jugular vein; convulsions, fell on the side; yet after 25 seconds it arose; recovered.

18. Weight, 410 gm.; 8 c.c. Fluid 16 into jugular vein; convulsions; fell on the side; dyspnea; after 1 minute it arose; recovered.

19. Weight, 455 gm.; 8 c.c. Fluid 15 into jugular vein; death in 7½ minutes; slight lung inflation; thrombus in right heart.

20. Weight, 360 gm.; 4 c.c. Fluid 21 into jugular vein. Death in 2½ minutes; strong lung inflation; thrombus in right heart.

21. Weight, 455 gm.; 4 c.c. of Fluid 22 into jugular vein; death in 2½ minutes; strong lung inflation and punctate hemorrhages under the pleura; thrombus in right heart. Before the injection 4 c.c. of blood were taken from the heart.

22. Weight, 386 gm.; 4 c.c. Fluid 23 into jugular vein; no effect during 5 minutes; then convulsions, dyspnea, and coma; then convulsions recommenced and were again followed by a deep comatous state which lasted 1 hour and 40 minutes. The pig died 2 hours and 10 minutes after the beginning of the experiment. Strong lung inflation; lung hemorrhages; no thrombus in heart. Punctate hemorrhages in the mucous membrane of stomach and intestines.

23. Weight, 385 gm.; 4 c.c. Fluid 25 into jugular vein; death in 2 minutes; slight lung inflation and punctate hemorrhages; thrombus in right heart. Before the injection 4 c.c. of blood were taken from the heart.

24. Weight, 405 gm.; 4 c.c. Fluid 25 into jugular vein; death in 2 minutes; no lung inflation; punctate hemorrhages and intense hyperemia; no thrombus in heart. Before the injection 4 c.c. of blood were taken from the heart.

25. Weight, 335 gm.; 4 c.c. Fluid 29 into jugular vein; death after 2 minutes; strong lung inflation; thrombus in right heart.

26. Weight, 340 gm.; 4 c.c. Fluid 28 into jugular vein; death after 2 minutes; strong lung inflation and capillary hemorrhages; thrombus in right heart.

27. Weight, 300 gm.; 4 c.c. Fluid 30 into jugular vein; death after 2 minutes and 15 seconds; slight lung inflation; thrombus in right heart.

28. Weight, 335 gm.; 4 c.c. Fluid 32 into jugular vein; death in 2 minutes; strong lung inflation; thrombus in right heart.

29. Weight, 330 gm.; 5 c.c. Fluid 29 into jugular vein; death after 25 minutes; strong lung inflation; no thrombus in heart.

RABBITS

1. Weight, 560 gm.; received 10 c.c. of Fluid 1 in ear vein; death followed after 2 minutes. No thrombus in the heart.
2. Weight, 670 gm.; received 5 c.c. of Fluid 1 in the ear vein; convulsions, from which the animal recovered very soon; after 45 minutes convulsions again for 9 minutes; dyspnea and death; thrombus in the right heart.
3. Weight, 560 gm.; received 5 c.c. of Fluid 1 in ear vein; death after 3 minutes; thrombus in the right heart.
4. Weight, 570 gm.; received 10 c.c. of Fluid 12 in the ear vein with no effect.
5. Weight, 495 gm.; received 10 c.c. of Fluid 6 in the jugular vein; death after 1½ minutes; thrombus in the right and the left heart.
6. Weight, 740 gm.; received 10 c.c. of Fluid 7 in the ear vein, with no effect.
7. Weight, 570 gm.; received 10 c.c. of Fluid 12 in the ear vein; death after 1½ minutes; no thrombus in the heart.
8. Weight, 490 gm.; received 4 c.c. Fluid 14 into the ear vein; death after 1½ minutes; thrombus in the right heart.
9. Weight, 590 gm.; received 4 c.c. of Fluid 25 in the ear vein; death after 5 minutes; thrombus in the right heart.

The necropsy of the guinea-pigs revealed the following picture: For the most part the lungs were so inflated that they filled the thorax entirely and covered the greatest part of the heart. They were immobile and did not collapse. A slight inflation or the complete absence of inflation was rather rare. In the majority of cases the lungs were hyperemic and of pale pink color. The hemorrhages, seen macroscopically, were not frequent; generally they were punctate. Sometimes I found in the emphysematous tissue slightly shrunken parts of normal not inflated lungs.

The microscopic examination revealed a marked dilatation of the alveoli (Fig. 1); the walls of the alveoli were frequently torn; the vessels and capillaries were for the most part in a state of intense hyperemia; in some cases the extension of the capillaries went so far that they looked like big spherical formations (Fig. 2) filled with real corpuscles; in this state ruptures of the walls occur.

The capillary hemorrhages seldom involved large parts of the lung tissue; when they did, this was from diapedesis and not because of excessive extension (Fig. 4). The contraction of the bronchial openings and the plaits and folds in the mucous membrane of the bronchi were present in the majority of cases, yet not always (Fig. 3).

In the right heart, and the vessels leading to it, thrombosis was frequent; now and then in the left heart also; sometimes there was none at all. If the necropsy was made immediately after death the heart was nearly always still beating, sometimes as long as 11 minutes. When there was thrombi in the heart, they appeared now and then also in the vena cava inferior.

The retardation of the coagulation of the blood was insignificant. The organs of the abdomen were full of blood, also the vessels of the mesentery; the gallbladder was frequently distended. In some cases capillary hemorrhages were observed in the mucous membrane of the stomach and the intestine.

As to the rabbits: their lungs were not inflated; for the most part the lungs were hyperemic. In the heart, thrombi were generally present, yet not always; often also in the inferior cava. The blood of the rabbits, contrarily to that of guinea-pigs, did not coagulate for a very long time, sometimes not for 24-36 hours. The organs of the abdomen were full of blood; the liver especially.

My experiments show that thrombosis was very frequent; in anaphylaxis it is said to be rarely found. Two reasons, however, do not allow a sharp demarcation between anaphylactic shock and the shock I observed. First of all, the formation of thrombus in the heart during life can be observed even in the conditions of a real anaphylactic experiment, if one injects into a fresh animal the immune serum against its own albumin, instead of injecting antigen into sensitized animals. Besides, the protocols show that thrombi were not present in all cases; so one cannot attribute the death to thrombosis of the heart and the vessels, moreover, the clinical phenomena are identic when thrombosis occurs and when it does not occur. Inflation and immobility of the lungs in connection with a specific clinical picture being considered as important signs of anaphylactic shock, I would emphasize that the condition of the lungs in my experiments entirely completes the series of analogies with anaphylactic shock. I mentioned that sometimes I did not discover any folds in the mucous membrane of the bronchi nor any contraction of the bronchial openings, but this may be the case even in anaphylaxis (Kumagai[6]).

Thus, on basis of the preceding argument, one may draw the conclusion that the clinical phenomena and the anatomic changes which accompany the shock caused by the injection of cotyledon fluid into the vein are those of the anaphylactic shock. From this one can infer that in order to provoke the clinical picture and the anatomic changes characteristic of anaphylactic shock, it is necessary to create in the animal organism the conditions which are indispensable in order to obtain precipitation in serum or lysis and agglutination of red corpuscles in vitro; and it is quite indifferent whether this effect is due to the previous immunization of the animal, which is the object of the experiment or which furnishes the immune serum, or to some substance quite independent of the animal the object of the experiment.

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[6] Ztschr. f. Immunitätsforsch., 1913, 17, p. 602.

EXPERIMENT 2

The experiments now to be described were undertaken in order to study the relation between the precipitating and agglutinating powers of the cotyledon fluid on the one hand, and its power to provoke the clinical picture of the anaphylactic shock on the other. It appeared plausible a priori that the fluid when deprived of all precipitating and agglutinating substances would be quite harmless for animals. The experiments fully confirmed this supposition. The procedure was as follows: First of all, I determined the fatal dose of the fluid of the plant; this quantity was mixed with a definite quantity of serum or bacterial mass which was directly washed off with the fluid from agar slants; after the development of precipitation or agglutination the sediment was separated from the liquid by means of centrifugation. The liquid was tested in order to ascertain whether it was completely devoid of precipitating and agglutinating substances, or not; finally, it was injected into the jugular vein in quantity equal to the fatal dose, or slightly surpassing it.

GUINEA-PIGS

All injections were made into the jugular vein.

1. Weight, 305 gm.; received 5 c.c. of fluid prepared with 10 c.c. of Cotyledon Fluid 8 + 2 c.c. of horse serum; no effect.
2. Weight, 310 gm.; received 5 c.c. of fluid made with 10 c.c. of Fluid 8 + 2 c.c. of horse serum; no effect.
3. Weight, 315 gm.; received 4.5 c.c. of fluid made with 7.5 c.c. of Fluid 8 + 2 c.c. of agar cultures of B. coli; no effect.
4. Weight, 345 gm.; received 6.5 c.c. of fluid made of 8 c.c. of Fluid 12 + 1 c.c. of horse serum; no effect.
5. Weight, 345 gm.; received 6 c.c. of fluid made of 8 c.c. of Fluid 12 + 3 cultures of B. coli; death followed after 1½ minutes; strong lung inflation; thrombus in the right heart.
6. Weight, 270 gm.; received 6 c.c. of fluid of 7.5 c.c. of Fluid 9 + 2 cultures of B. coli; no effect.
7. Weight, 370 gm.; received 5 c.c. of fluid made of 10 c.c. of Fluid 14 + 2 c.c. of horse serum; no effect during one minute; then followed the usual picture of shock. At the end of the deep comatose state a bloody foam came

from mouth and nostrils. The lung inflation was insignificant; many hemorrhages in the lungs; edema; no thrombus in the heart; death after 3½ minutes.

8. Weight, 290 gm.; received 10.8 c.c. of fluid composed of 10 c.c. of Fluid 14 + 8 c.c. of horse serum. Brief convulsions; after 20 minutes the animal was quite recovered.

9. Weight, 345 gm.; received 10 c.c. of mixture of 10 c.c. of Fluid 15 + 1 c.c. of horse serum; convulsions and dyspnea; then slow recovery.

10. Weight, 300 gm.; received 10 c.c. of Fluid 15 treated with 4 tubes of B. coli slant agar. Usual phenomena and death after 3 minutes; strong lung inflation; thrombus in the right heart.

11. Weight, 310 gm.; received 8 c.c. of fluid composed of 10 c.c. of Fluid 14 + 1 c.c. of horse serum; usual picture; a bloody foam came from mouth and nostrils; intense lung inflation; hemorrhages; edema; death after 4 minutes.

12. Weight, 370 gm.; received 5 c.c. of fluid composed of 10 c.c. of Fluid 21 + 3 c.c. of horse serum; no result during 8 minutes; then the usual phenomena of shock; death after 7 minutes. Intense lung inflation; several hemorrhages under the pleura; thrombus in the right heart.

13. Weight, 310 gm.; received 8 c.c. of fluid composed of 10 c.c. of Fluid 21 + 10 c.c. of horse serum; no effect.

14. Weight, 450 gm.; received 4.8 c.c. of fluid composed of 5 c.c. of Fluid 22 + 1 c.c. of horse serum; no effect.

15. Weight, 360 gm.; received 4 c.c. of Fluid 25 + 3 c.c. of horse serum; no effect.

16. Weight, 320 gm.; received 5 c.c. of fluid composed of 4 c.c. of Fluid 29 + 7 c.c. of horse serum; no effect.

17. Weight, 320 gm.; received 4 c.c. of fluid composed of 11 c.c. of Fluid 29 + 10 agar cultures of B. coli; no effect.

18. Weight, 300 gm.; received 4.5 c.c. of fluid of 10 c.c. of Fluid 30 + 10 agar cultures of B. coli; no effect.

19. Weight, 305 gm.; received 4.5 c.c. of Fluid 32 + 8 cultures of B. coli; no effect.

Thus, in the majority of cases the disappearance of the precipitating and agglutinating substances deprived the cotyledon fluid of the power to cause shock in the animal. In 5 animals only was shock and death provoked, in spite of the precipitating and agglutinating substances having been removed from the cotyledon fluid. These cases sometimes offered the picture of lung edema and of diffuse hemorrhages, revealed by the foaming bloody liquid which came from mouth and nostrils. Lung edema is observed also in anaphylaxis (Kumagai[6]). I must try to give an explanation of these cases.

Studying the precipitating action of the cotyledon fluid I discovered a phenomenon in some degree analogous with those observed by Danysz, Bordet and v. Dnngern in their experiments of neutralization of toxins by antitoxins. If 4 c.c. of cotyledon fluid were mixed at once with 1 c.c. of horse serum (samples 22, 23, 24 and 25) and separated from the sediment by means of centrifugation, further additions of serum did not provoke any new precipitation; if only 1 c.c. of fluid was taken, and the serum was added by drops, the quantities of serum causing precipitation were the following: for Fluid 22—0.5 c.c., 23—0.8 c.c., 24—0.6 c.c., and 25—0.5 c.c. It results from this that 1 c.c. of horse serum was insufficient for the complete extraction of all the precipitating substances from 4 c.c. of fluid; 2.0, 3.2, 2.4 and 4.0 c.c. of serum were necessary for that purpose. Thus, to speak exactly, in the majority of my experiments I did not deprive the fluid of all its precipitating substances; a part of them was left, and though this remaining part was unable to generate any further precipitation in vitro, in vivo it might have conserved the power to change the degree of the disperseness of the plasma colloids and to cause shock and death in this way. In fact, the fluid treated with large quantities of serum had no action on the animals, while the same fluid treated with the quantities that I generally used in the experiments killed the guinea-pigs (refer to experiments with Fluids 14 and 21). It is probable that all this may be affirmed also of the agglutinating substances of the cotyledon fluid (note experiments with Fluids 12, 15, 30 and 32).

Referring to parallelism between the action of the fluid in vitro and in vivo, I have not the intention to affirm that the fluid provokes in the animal agglutination of blood corpuscles, or precipitation in the plasma similar to that in the serum. Yet, the indispensableness of precipitating substances in the fluid for the production of shock suggests the idea that in the blood system of animals the fluid changes always the degree of the disperseness of the plasma colloids, and thus causes shock and death. In vitro the change of the disperseness of the serum colloids always causes the visible formation of gel under the form of precipitate; in the animal the formation of gel seen with the eye under the form of thrombus is not always observed.

On the basis of the results given one may conclude that the cotyledon fluid provokes a shock, which offers a clinical picture and anatomic changes analogous to those of anaphylactic shock; the shock and the death of the animal are due to change in the degree of disperseness of the plasma colloids, and it is indifferent whether this change causes the formation of thrombus or not.

EXPERIMENT 3

The experiments now described corroborate the supposition that the power to provoke the shock and death of animals of the active substance of the fluid is due to a physicochemical influence over the blood circulating in the vessels, and not to a chemical injury of some cells of the organism. The fluid injected into the abdomen of guinea-pigs did not affect them at all; neither did a subcutaneous injection.

I studied the chemical nature of the active substance of the cotyledon together with J. D. Sartakoff, but the circumstances of the war did not allow us to finish that work. This may be stated: the substances of the fluid which cause the agglutination of the bacteria and the red blood corpuscles, the precipitation of serum, the hemolysis of blood corpuscles, the shock and death of animals, are either glucosids, or they pass during precipitation into the sediment together with glucosids, because of the great absorbing faculty of the latter. Under the action of a weak soda solution the active substances of the cotyledon fluid pass into the precipitate; this precipitate being again dissolved in a weak solution of acetic acid, the active substances do not lose their various powers.

GUINEA-PIGS

1. Weight, 325 gm.; received 10 c.c. of Fluid 5 into the abdomen with no effect.
2. Weight, 300 gm.; received 6 c.c. of Fluid 22 into the abdomen with no effect. On the 3rd day it died of purulent peritonitis.
3. Weight, 350 gm.; received 5 c.c. of Fluid 25 into the abdomen; no effect.
4. Weight, 460 gm.; received 10 c.c. of Fluid 24 into the abdomen with no effect.

EXPERIMENT 4

Not only were the symptoms and the anatomic changes of the shock observed in my experiments those of anaphylaxis as shown by Experiment 4, but the injection of the cotyledon fluid under the skin of animals provokes the condition known as Arthus' phenomenon, ordinarily considered as anaphylactic and to presuppose an earlier sensitization of the animal and a subsequent injection of antigen.

GUINEA-PIGS

1. Weight, 295 gm.; 4 c.c. of Fluid 22 under the skin of the abdomen; after 24 hours the place of the injection showed edema; after 48 hours the infiltrate grew hard and painful; after 144 hours a placque was formed with ulceration at the margins; after some time this became covered with a crust and finally cicatrized.
2. Weight, 310 gm.; 5 c.c. of Fluid 25 under the skin; edema after 24 hours; after 48 hours a hard infiltrate, which grew smaller after 72 hours and slowly disappeared during the following days.
3. Weight, 385 gm.; 5.25 c.c. of Fluid 30 under the skin of the abdomen; edema after 24 hours; after 48 hours a firm infiltrate, which became doughy

after 96 hours; on pressure it burst open and discharged bloody material; after 144 hours the infiltrate was hard, 6 by 4 cm.; later it was covered with a crust and cicatrized.

4. Weight, 385 gm.; 5 c.c. of Fluid 32 under the skin of the abdomen; there was almost the same picture as in the preceding animals.

RABBITS

1. Weight, 485 gm.; received 4 c.c. of Fluid 29 under the skin of the abdomen; after 24 hours—edema, which increased after 48 hours and grew hard; during the following days it increased still more and attained the firmness of cartilage; its surface became mortified after 288 hours and formed a crust covering a hard mass, which cicatrized afterwards; the scar was starlike.
2. Weight, 560 gm.; received 4 c.c. of Fluid 29 under the skin of the abdomen; there was nearly the same picture as in the preceding case.
3. Weight, 490 gm.; 5 c.c. of Fluid 28 under the skin of the abdomen; edema after 24 hours; after 48 hours a hard infiltrate; its center became mortified after 72 hours; after 144 hours there was a large crust covering a hard area, which cicatrized afterwards.

DIMINUTION OF COMPLEMENT

It is known that Friedberger[7] and workers in his laboratory attach much value to the diminution of the quantity of complement in the state of anaphylaxis, and this fact is cited to confirm their theory of anaphylactic shock being a consequence of the intoxication of the organism with the products of the parenteral digestion of the antigen by the antibodies, with participation of the complement; the latter is partially consumed during the process. The investigations of Busson and Takahashi[8] proved that sometimes there is not observed any decrease of the quantity of complement in the state of anaphylaxis. In my experiments I discovered a diminution of the quantity of complement nearly always during the shock. The complement titer was determined just before the beginning of the experiment, the blood being taken from the heart and immediately after the death. The results of the titration are shown in Table 1. The total quantity in each tube was 2.5 c.c.; 0.5 c.c. of a 5 % suspension of blood corpuscles, and a triple hemolytic dose of a serum with a titer of 1 : 1200 (0.5 c.c.); incubation 30 minutes at 37 C.

In the condition of my experiments the presence of antibodies was excluded; therefore, I believe that the cause of the diminution of the quantity of complement during the shock (and probably during anaphylaxis too) is to be explained in some other way than that of Friedberger. In my opinion, it is more plausible that the complement might be absorbed from the plasma by some substances of the plasma, which show a decrease of their degree of disperseness.

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[7] Ztschr. f. Immunitätsforsch., 1909, 3, p. 581.

[8] Zentralbl. f. Bacteriol., O., I, 1912, 65, p. 146.

TABLE 1

DIMINUTION IN COMPLEMENT AFTER SHOCK

Experiment	Guinea-Pigs	When Complement Was Obtained	Hemolytic Power of the Guinea-Pig Complement				
			0.01 C.c. of Amboceptor	0.03 C.c. of Amboceptor	0.05 C.c. of Amboceptor	0.07 C.c. of Amboceptor	0.09 C.c. of Amboceptor
1	13	Before the experiment	Slight hemolysis	Incomplete hemolysis	Complete hemolysis	Complete hemolysis	Complete hemolysis
		After the experiment	No hemolysis	No hemolysis	Incomplete hemolysis	Incomplete hemolysis	Incomplete hemolysis
1	14	Before the experiment	Slight hemolysis	Complete hemolysis	Complete hemolysis	Complete hemolysis	Complete hemolysis
		After the experiment	No hemolysis	Slight hemolysis	Almost incomplete hemolysis	Complete hemolysis	Complete hemolysis
1	15	Before the experiment	Incomplete hemolysis	Complete hemolysis	Complete hemolysis	Complete hemolysis	Complete hemolysis
		After the experiment	No hemolysis	Almost complete hemolysis	Complete hemolysis	Complete hemolysis	Complete hemolysis
1	21	Before the experiment	Slight hemolysis	Complete hemolysis	Complete hemolysis	Complete hemolysis	Complete hemolysis
		After the experiment	No hemolysis	Incomplete hemolysis	Almost complete hemolysis	Almost complete hemolysis	Almose complete hemolysis
1	23	Before the experiment	Incomplete hemolysis	Complete hemolysis	Complete hemolysis	Complete hemolysis	Complete hemolysis
		After the experiment	No hemolysis	No hemolysis	Almost complete hemolysis	Almost complete hemolysis	Almost complete hemolysis
1	24	Before the experiment	Slight hemolysis	Almost complete hemolysis	Complete hemolysis	Complete hemolysis	Complete hemolysis
		After the experiment	No hemol-hemolysis	Slight hemolysis	Incomplete hemolysis	Almost complete hemolysis	Almost complete hemolysis
	92*	Before the experiment	Slight hemolysis	Incomplete hemolysis	Complete hemolysis	Complete hemolysis	Complete hemolysis
		After the experiment	Slight hemolysis	Slight hemolysis	Slight hemolysis	Slight hemolysis	Slight hemolysis
	92*	Before the experiment	Slight hemolysis	Complete hemolysis	Complete hemolysis	Complete hemolysis	Complete hemolysis
		After the experiment	No hemol ysis	Incomplete hemolysis	Incomplete hemolysis	Incomplete hemolysis	Incomplete hemolysis

* Not mentioned in Exper. 1.

DISCUSSION

I believe that the data given prove with sufficient probability that the substances provoking the change of the degree of disperseness in a serum or a suspension of bacterial or animal cells in vitro have the same effect in an animal body, when directly introduced into the blood system, and the result is a shock exactly reproducing the anaphylactic, clinically and anatomically.

My experiments fully corroborate the data of Doerr and Moldovan[9] who obtained a shock similar to the anaphylactic by injecting a water colloidal solution of silicic acid, also of nucleinic acid, and of dialyzed iron hydroxid.

The anaphylactic shock supposes the previous immunization of the animal, and the immune bodies cause the same change in the degree of disperseness in vitro as substances of the cotyledon fluid which I used; it is, therefore, quite natural to suppose that the shock observed in anaphylaxis and related processes just as the shock studied in the present investigation, is due to change in the degree of disperseness of the plasma colloids of the blood. On this account one may qualify all these processes — and others showing an analogous, clinical and anatomic picture — as morbid processes caused by change of the degree of disperseness of the blood plasma. These processes may be grouped as follows:

A. In an immunized organism—

1. Active anaphylaxis.

B. In a not immunized organism, caused by immune serum—

I.—1. Passive anaphylaxis.

2. Shock due to serum against the albumin or the red corpuscles of the animal submitted to experiment.

3. Shock due to hemolytic sheep serum in animals whose organs contain heterogeneous sheep antigen.

4. Shock due to a mixture of antigen and antibody.

II.—Caused by substances of animal origin—

1. Shock due to some normal serum (ox).

2. Shock after the injection of fresh defibrinated blood and of the serum of that blood, or not coagulated blood collected into a paraffined vessel.

3. Shock after the injection of an extract of animal organs, or of the suspension of these organs in physiologic salt solution.

4. Shock after the injection of urine.

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[9] Bioch. Ztschr., 1912, 41, p. 27.

5. Shock after the injection of fresh serum treated during some time with bacteria, animal cells, agar, kaolin, etc. (anaphylatoxin).

III.—Caused by substances of unknown chemical origin or by chemical substances—

1. Shock due to substances found in Cotyledon scheideckeri.

2. Shock due to water colloidal solution of silicic acid, nucleinic acid, or dialyzed iron.

This classification has no claim to completeness.

CONCLUSIONS

The sap of a plant, Cotyledon scheideckeri, which is able to precipitate animal serum, and to agglutinate and cause lysis of red blood corpuscles, has the power to provoke the symptoms and the anatomic changes characteristic for anaphylactic shock, when introduced into the veins of animals.

The injection of the cotyledon fluid under the skin of animals provokes phenomena identical with the local anaphylaxis, known as Arthus' phenomenon.

When deprived of all precipitating and agglutinating substances, the fluid is quite harmless for animals.

The shock and the death after injection of the cotyledon fluid are due to change in the degree of the disperseness of the plasma colloids.

In anaphylactic shock in immunized animals immune bodies cause the same change in the degree of disperseness in vitro substances in the cotyledon juice which I examined; it is, therefore, quite natural to suppose that the shock observed in anaphylaxis and related processes just as the shock studied in the present investigations are due to change in the degree of disperseness of the plasma colloids of the blood. On this account one may regard all these processes — and others, showing analogous, clinical and anatomic changes — as morbid processes caused by a change of degree of disperseness of the blood plasma.

EXPLANATION OF PLATE 4

Figs. 1 and 2. The alveoli are distended; some of them have torn walls; the capillaries are in a state of strong hyperemia. Exper. 1, Guinea-Pig 20.

Fig. 3. The alveoli are distended; some of them have torn walls. The opening of one bronchus is narrowed; the other bronchus does not possess smooth muscles, and therefore is not contracted. Exper. 1, Guinea-Pig 25.

Fig. 4. The alveoli are distended; some of the walls are torn. Hemorrhages from capillaries per diapedesin. Exper. 1, Guinea-Pig 21.

PLATE 4

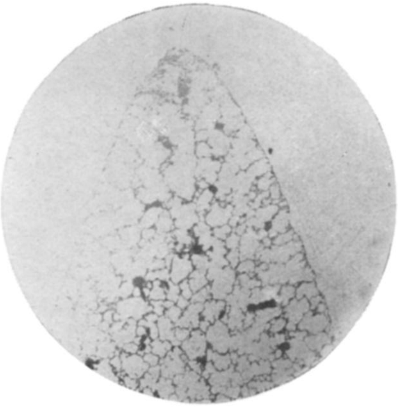
FIG. 1.

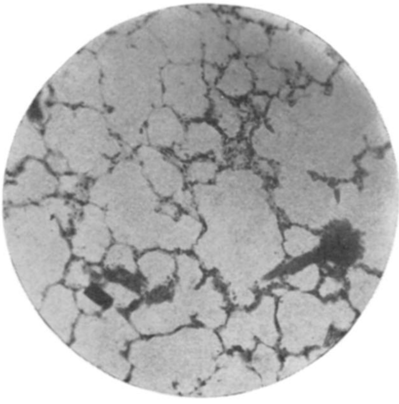
FIG. 2.

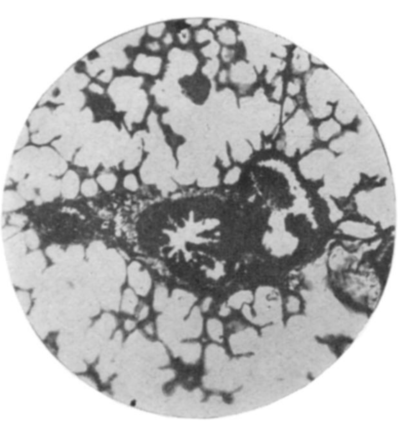
FIG. 3.

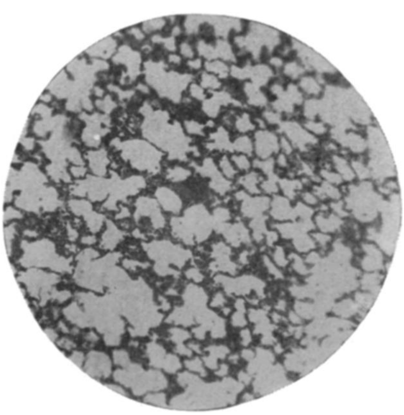
FIG. 4.